

HEMANGIO-ENDOTHELIOMA: A TUMOR OF BLOOD VESSELS FEATURING VASCULAR ENDOTHELIAL CELLS

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ACCORDING to Shaw (1928), blood vessels are formed in the embryo from angioblastic endothelial cells developing in the vascular layer of the mesenchyme. These cells first form solid cords and islands; lumens then appear in them and, finally, the isolated structures unite to form continuous tubes. If some of these structures fail to unite and remain segregated, they may grow independently and form hemangiomas which may subsequently unite with normal blood vessels or remain separated from them. They may remain as simple capillary tubes consisting of endothelial lining cells surrounded by a delicate reticulin framework or have, in addition, other cells normally associated with blood vessels, such as smooth muscle cells and pericytes, and also, on occasion, other tissues such as fat, smooth muscle, myxomatous tissue, bone, mature and immature red and white blood cells and perhaps other cells which may be derived from mesenchyme.

This accounts for the focal origin of a large majority of vascular tumors but it does not account for all, nor does it explain the spread and infiltrative growth of any of these tumors after they have once formed. This takes place by a process similar to the formation of capillaries in granulation tissue which occurs by the sprouting of endothelial cells from preexisting capillaries forming first a solid cord which secondarily becomes canalized. It seems probable that the malignant tumors in this series, which appeared in traumatized areas (Cases 8 and 14), must have developed in this fashion from the capillaries of granulation tissue. Probably all of the malignant tumors exhibit this type of growth in their infiltrative growth.

These methods of development make possible a very wide variety of gross and microscopic forms which have been endlessly described and named by pathologists, dermatologists, neurologists, and many others. It often leads to the formation of multiple tumors. Usually such tumors, even if they appear successively and grow to a large size, are not suspected of being malignant growths, but a few cases have been recorded whose behavior has raised this question. In some, such as the cases of Glogengiesser (1939), Rabson (1938), Weiss (1911) in humans, and Sal (1931) in chickens, growth of vascular and related tissues occurred in widespread areas, as if it were due to a profound and perhaps systemic disturbance of the vascular system akin to von Recklinghausen's disease in the nervous system. If Kaposi's disease is neoplastic, it probably belongs to this group. In another group of cases, what have been described as benign hemangiomas have developed in one area

with the subsequent appearance of hemangiomas or hemangio-endotheliomas in other areas, as if they were metastases. This phenomenon has given rise to the term benign metastasizing hemangioma. The writer has never observed such an anomaly in his own material, and questions its occurrence. The subject will be discussed later in this paper.

In spite of the fact that blood vessels are ubiquitous, and benign vascular tumors exceedingly common, malignant tumors of blood vessels are exceedingly rare. Just how many of them have been recorded is impossible to say because many tumors have been reported as such with insufficient or obvi-

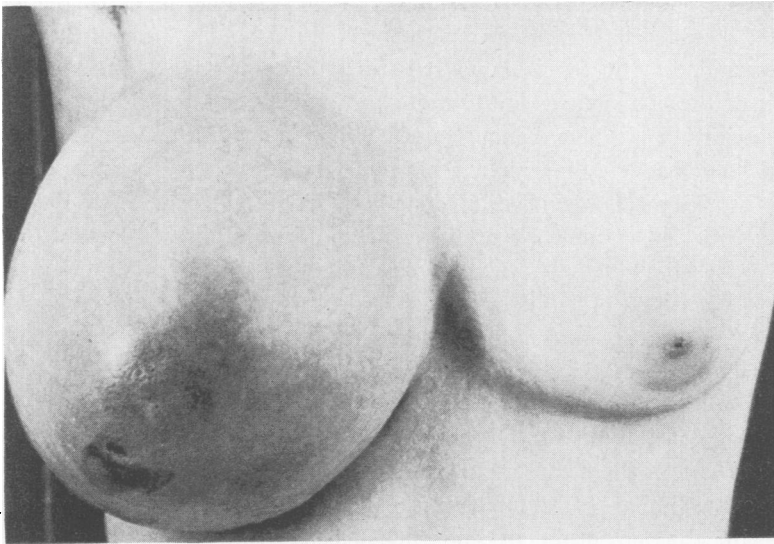


FIG. 1.—Case 1: Hemangio-endothelioma of the mammary gland in a 19-year-old girl, 14 months after onset, just before it was removed. The enormously enlarged bluish, turgid right breast weighed 1647 Gm., and contained a liter of blood.

ously erroneous data. After reading reports of 118 cases labelled with some name suggestive of a malignant vascular tumor, the writer felt compelled to reject 41, or 35 per cent of them, either because there was an inadequate or no histologic report, or because, in his opinion, the illustrations and text described a tumor of some other kind.

There are certainly two, and probably three, malignant vascular tumors all characterized by the formation of vascular tubes but with different cells playing a dominant rôle in tumor growth. Attention has already been called to the group featuring the pericyte (Murray and Stout, 1942; Stout and Murray, 1942) for which the name hemangiopericytoma has been suggested. This group includes the glomus tumors, and the vast majority of them are benign. However, two cases have shown aggressive infiltrative growth, and at least one other is known to have metastasized—establishing the existence of a malignant variant.

Since smooth muscle forms an important part of many blood vessels, one might expect to find a vascular form of leiomyosarcoma. There is a benign

vascular leiomyoma (Stout, 1937, 1938), hence from the theoretical viewpoint, there is no reason why there should not also be a malignant form of this tumor. The evidence that such a neoplastic type exists is scanty. Fourmestreaux and Foulon (1930), Grandclaude, Lambert and Driessens (1933), Leuret *et al.* (1930), and König (1921), believe that such tumors occur. The case reported by Leuret, and his associates, seems to have been composed of both atypical smooth muscle and many vessels, sometimes with heaped-up irregular endothelia and may, indeed, be truly compounded of both of these elements. It would be preferable to obtain further confirmation from others before accepting this as a definite type and not just a sport. This writer has not encountered such a tumor.

The third group is much better known and contains the majority of the malignant vascular tumors. It also forms vascular tubes but the important cell responsible for its aggressive growth and metastases is the endothelial cell. Because of this, it is best called by the name hemangio-endothelioma, devised by Mallory (1908), which is properly descriptive and has the added advantage of familiarity.

The writer has had the good fortune of assembling 18 such tumors from various sources, which he is permitted to present in a group through the generosity of several different pathologists and surgeons. Such a collection affords a better opportunity to study the characteristics and peculiarities of this tumor type than can be gained by attempting to analyze and collate the literature, for the reasons already indicated. The writer will base most of his remarks upon this material and only supplement it when necessary from the reports of others.

Eleven of the patients here reported were females and seven males. Three of them were colored. The age at onset varied from birth to 66 years; nine were less than 30 years of age but six were over 50 years. A tumor of the popliteal space (Case 14) and the one in the erector spinae muscles (Case 8) developed in traumatized areas.

The distribution of the primary lesions is shown in Table I.

TABLE I
PRIMARY SITES OF HEMANGIO-ENDOTHELIOMAS

Mammary gland.....	3	Pleura.....	1	Skin and subcutaneous tissues } 6
Liver.....	2	Uterus.....	1	
Bones.....	2	Orbit.....	1	
Striated muscles.....	2			

The majority of reported cases have been in the spleen, the liver, the bones, or in the skin and subcutaneous tissues. In acceptable reports of others can be found the following additional primary sites mentioned: Tonsil (de Bary, 1935); stomach (Sherrill and Graves, 1915); intestine (Magnusson, 1934); omentum (Ransom and Samson, 1934); retroperitoneal space (Beitzke, 1932; Leubner, 1935; Cannata, 1931); lung (Hall, 1935; Plaut, 1930); mediastinum (Shennan, 1914); heart (Gross and Englehart, 1937; Hewer and Kemp, 1936); pericardium (Scheidegger, 1937); ovary (Sovak

and Carabba, 1931); corpora cavernosa (Foulds and Flett, 1938); central nervous system (Turner and Kernohan, 1941).

The malignant nature of these tumors is fully confirmed by the outcome of the cases in this group. Of the 18 patients, ten are known to have died with metastases; one was last seen with local persistence of disease; one had had nine operations for local reappearances and was not followed after the

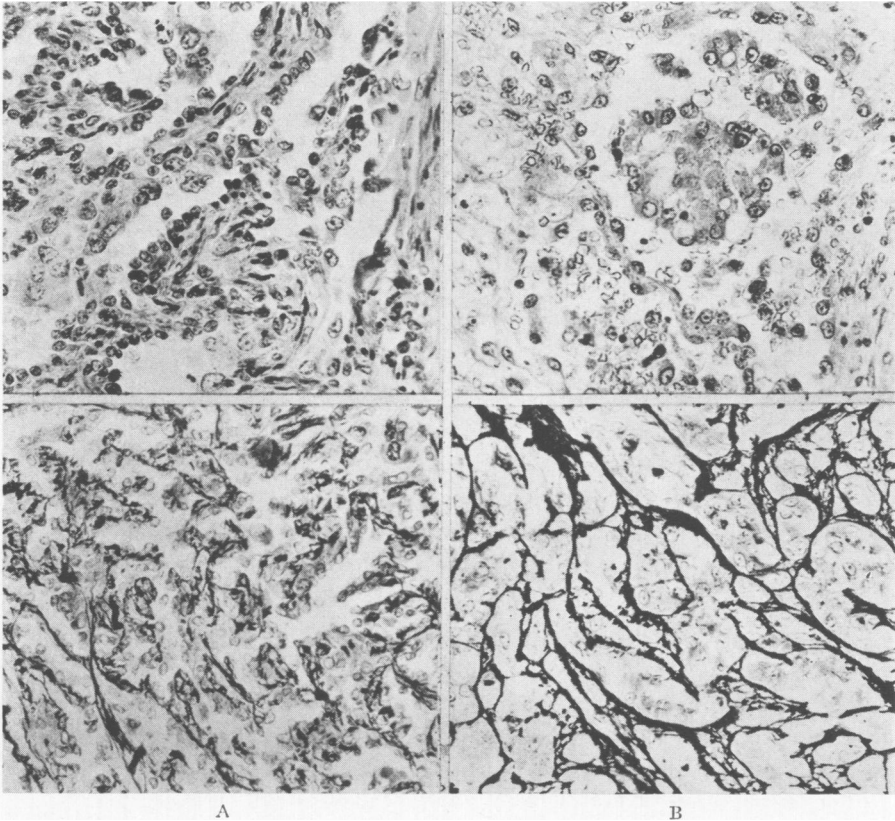


FIG. 2.—Case 13: A (left). Hemangio-endothelioma of supraclavicular region. Anastomosing vascular channels lined by heaped-up, rounded atypical endothelia. Silver reticulin stain below outlines the vascular tubes.

Case 14: B (right). Hemangio-endothelioma of popliteal region. Poorly defined vascular channels lined by swollen polygonal endothelia are shown above, while below the silver reticulin stain accentuates the vessels by blackening their supportive framework (see Fig. 9). ($\times 5.25$ reduced)

last operation; three patients are without evidence of tumor 8, 12, and 30 months after removal; two were not followed; and only one is known to be well five years and two months after excision of a popliteal tumor.

As in other malignant tumors, the course of the disease is sometimes fulminating, as shown by Case 2, the 65-year-old woman, who was dead eight weeks after she first noticed a growth in her breast; and sometimes exceedingly protracted, as exemplified by Case 16, who during the first 19 years of her life had had a persistently growing tumor of the upper eyelid which constantly recurred in spite of eight attempts to remove it (Figs. 10 and 5 B).

The vascular nature of these tumors can generally be appreciated when one approaches them, and they have a tendency to bleed either into themselves or externally if they penetrate through a body surface. An example of the former condition is furnished by Case 1, the 19-year-old girl, with a tumor in the mammary gland which contained a liter of blood in it (Fig. 1). This bleeding was associated not only with a severe anemia but a purpura, with platelets averaging only 51,000. An example of surface bleeding is furnished by the uterine tumor (Case 10) which bled with increasing severity over a two-year period. On the other hand, Case 18 gave no evidence of its vascular composition even when excised, and only microscopic examination revealed its true nature. It developed in the eyebrow of a three-months-old boy, and was mistaken for a dermoid cyst.

Great vascularity and hemorrhages, while they may suggest a tumor of blood vessels, are not in themselves sufficient to prove that a neoplasm is indeed a malignant tumor of vascular elements. Both Molotkoff, (1933) and Ogilvie and MacKenzie (1936), have pointed out that chorio-epithelioma can be confused with blood vessel tumors and every experienced pathologist will recall extremely vascular hemorrhagic malignant tumors of other types. The diagnosis must, therefore, rest upon the histologic characteristics. These display themselves in a variable fashion and require presentation in some detail.

There are two features of the growth of hemangio-endothelioma which are striking and uniformly present in all true tumors of this kind, although they are sometimes masked and require differential staining clearly to demonstrate them. These are: First, the formation of atypical endothelial cells in greater numbers than are required to line the vessels with a simple endothelial membrane; and, second, the formation of vascular tubes with a delicate framework of reticulin fibers and a marked tendency for their lumens to anastomose. No tumor should be considered a hemangio-endothelioma unless these criteria are both present. The variations found are due to the marked variability in the number, shape, size and tinctorial peculiarities of the malignant endothelia. They may be irregularly rounded or polygonal (Figs. 2 A and B), or they may maintain an elongated shape (Figs. 3 and 4); they may form only a single continuous layer (Figs. 3 B and C), or they may become heaped up and more or less fill the lumen (Fig. 5 A). Usually they remain within the vascular tubes but occasionally they grow outside of it and form solid sheets of cells (Figs. 4 A and B). Whatever their shape, the tumor cells always differ from the endothelial cells of simple benign angiomas and normal blood vessels, although occasionally the blood vessels which are formed in the process of organization of a thrombus may simulate their appearance. It is usually easy to perceive that a tumor is composed of vascular tubes which tend to anastomose and are lined by atypical endothelia. When there is doubt about these things with ordinary stains, the relationships can be clarified by the use of a silver reticulin stain. This will cause the tubes

to stand out in sharp relief because each one, even in the most malignant tumor, has a delicate fibrous supporting framework and the silver brings out a distinctive pattern (Figs. 2, 3, 4 and 5). This pattern will be revealed with silver even when, with other stains, it is entirely obscured by an overgrowth of cells (Fig. 4 B). When ordinary stains make it impossible to decide

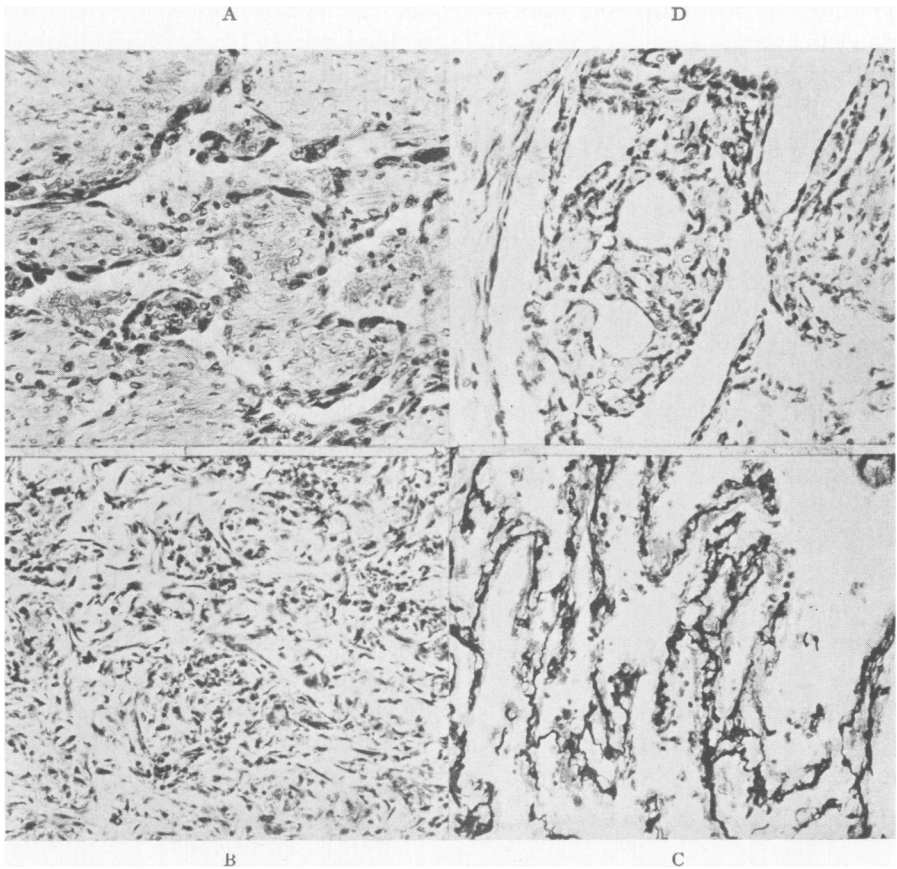


FIG. 3.—Case 10: A (upper left). Hemangio-endothelioma of uterus. Infiltrative extension of anastomosing blood vessels lined with bizarre elongated endothelia through the myometrium.

Case 6: B (lower left). Hemangio-endothelioma of tibia. Proliferation of anastomosing capillaries lined with hyperchromatic endothelia in the marrow.

Case 3: C (right). Hemangio-endothelioma of breast. Complex formation of vascular channels lined with hyperchromatic endothelia. The Laidlaw silver reticulin stain shown below accentuates the vascular pattern. ($\times 525$ reduced)

whether cells are grouped inside or outside of a vessel wall, and so to determine whether one is dealing with endothelia or pericytes, silver staining of the vascular reticulin sheath shows the exact relationship of the cells beyond peradventure (Fig. 5 A).

If one tries to group these tumors in order to give them descriptive subtitles, one encounters almost insuperable difficulties, for the cellular appearance and make-up not only may vary in different parts of the same tumor but also in its recurrent or metastatic manifestations. Some features, however, deserve special emphasis.

One variety of this tumor manifests a certain degree of constancy in its form. It seems to grow especially in infants, and there are two examples of it represented in the present series (Cases 17 and 18), both of which closely resemble one another in every way. These tumors differ from all of the others in that they both maintain a uniform histologic appearance throughout (Fig. 5 A), so that the illustration furnishes an accurate picture. They are composed of closely packed capillaries, with heaped up endothelia, and a tendency to anastomose, so that they are by definition hemangio-endotheliomas, but growth, although rapid, is orderly, and neither has recurred nor metastasized in the short space of time they have been followed. Nevertheless, one must not assume that this special form always pursues such a benign course. The kindness of Dr. Beryl Paige, Pathologist of the Babies Hospital, has enabled the writer to review the slides of the case of a female baby dying in its fifth month, which was reported by the late Dr. Martha Wollstein (1931) as a "malignant hemangioma of the lung with multiple visceral foci." In this case there were many tumors in skin and viscera, the majority of which were exactly similar to the two tumors here reported, while the rest were simple capillary or cavernous hemangiomas. It is really impossible to decide whether these tumors are multiple independent growths, as seems probable, or whether some of them are metastases. The question of metastasis of a simple hemangioma does not here arise, for the growths are definitely hemangio-endotheliomas.

At this point, it seems pertinent to debate the question of the so-called benign metastasizing hemangiomas. The writer reread the published reports of some of these cases in an effort to determine whether or not he could agree with the authors that the tumors were simple hemangiomas and that they metastasized. The cases of Langhans (1879), Borrmann (1907), Shennan (1914), Wright (1928), and Siirala and Näätänen (1940), all show atypical endothelia and very free vascular anastomoses, which bring them definitely into the class of hemangio-endothelioma. The cases of Weiss (1911), Konjetzny (1912) and Ewing (1928), are not illustrated with photomicrographs, so that the reader cannot judge for himself. Stamm's (1891) thesis was not available.

Robinson and Castleman (1936) reported that the primary tumor in their case was a simple hemangioma, while the metastases were angiosarcomatous. Their illustrations support this contention. It seemed important to review this case to determine whether or not the whole primary tumor appeared like the illustration. Dr. Castleman was kind enough to permit me to examine the original microscopic preparations. They show that in the primary growth there are some areas with extremely free-sprouting and anastomosis of capillaries which are lined with prominent darkly stained endothelia varying in relative size. Thus this case also shows features which lead me to classify it as hemangio-endothelioma and not simple benign hemangioma.

In the present group of tumors, Case 1, which has been reported previously,

with illustrations, by Hill and Stout (1942, Case 25), showed in the primary tumor the formation of a meshwork of anastomosing capillaries lined with deeply stained swollen endothelia, which resemble Robinson and Castleman's tumor and that of Borrmann, and are like Case 3 shown here in Figure 3 C. Such formations do not occur in simple nonmalignant hemangiomas. The picture may be reproduced occasionally in the very rapid formation of capil-

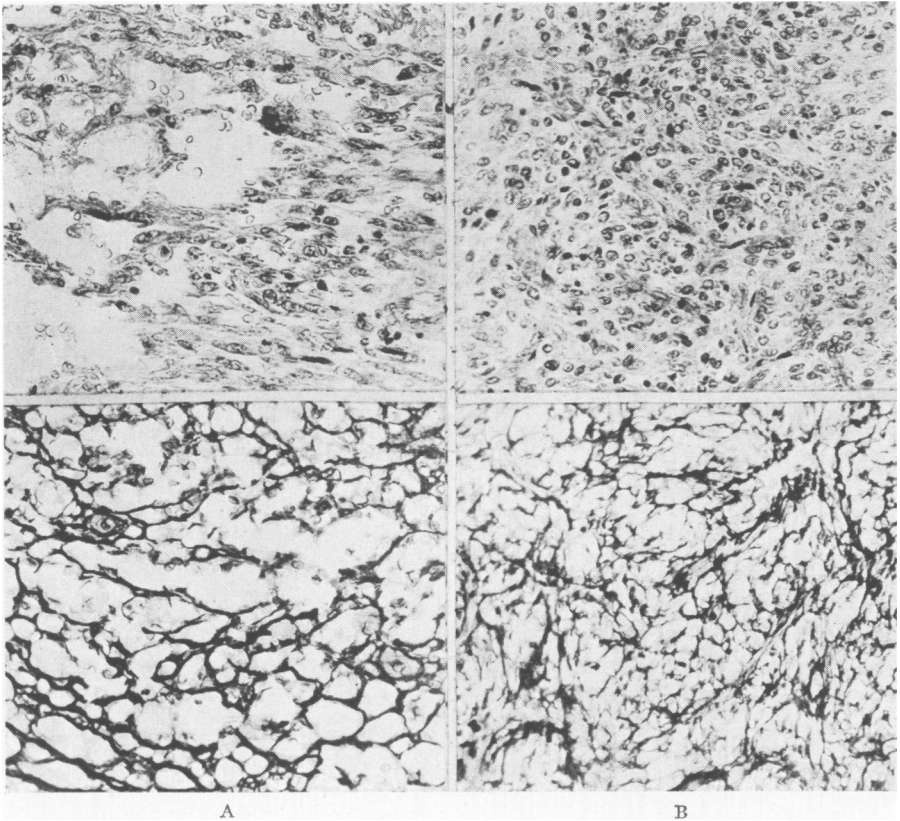


FIG. 4.—Case 8: A (left). Hemangio-endothelioma of erector spinae muscle. Above, the vascular pattern is partly obscured by the sheet-like proliferation of elongated endothelia, but the Laidlaw silver reticulin stain, below, demonstrates its presence.

Case 9: B (right). Hemangio-endothelioma of calf muscles. The endothelia of this tumor form solid cords of cells coursing in various directions. Laidlaw's silver reticulin stain, below, brings out the vascular pattern (see Figs. 6 and 7). ($\times 525$ reduced)

laries which can take place in the organization of intravascular thrombi. But here the growth is strictly limited to the thrombus and never invades surrounding tissues. This comparison emphasizes the fact that in malignant vascular tumors growth takes place by sprouting in the fashion characteristic of the formation of vessels in granulation tissue and not in the way blood vessels are developed in the primitive mesenchyme of the embryo.

Thus, the writer has not been able to find any case which, to him, offers incontrovertible proof of the existence of such an anomaly as a benign metastasizing hemangioma and he, therefore, doubts its existence.

One tumor (Case 9) in this series differs from all the others because the whole tumor is overgrown with elongated cells generally arranged in slender cords which are usually solid but sometimes have a core of red blood cells. In addition, capillaries lined with normal endothelia are frequent in some areas. Laidlaw's silver reticulin stain shows a vague tubular arrangement of reticulin corresponding with the solid cords of cells (Fig. 4 B). Grossly, this tumor was extremely vascular and hemorrhagic (Fig. 7). The morphologic features of this tumor alone would hardly warrant its inclusion in the group of hemangio-endotheliomas. It seems proper to do so, however, because explanation *in vitro* demonstrated that the tumor cells had the characteristics of endothelia. Details are reported in a separate communication (Murray and Stout, 1943).

In all of the tumors here described, and in acceptable previously reported cases, the tumor cells appear as variously illustrated in this paper. There are a few tumors of bone called angio-endotheliomas which have cells of a different aspect. These demand separate discussion.

On page 362 of the 4th Edition of Ewing's "Neoplastic Diseases" there appears an illustration (Fig. 133) labelled "Structure of angio-endothelioma of bone." It shows large clear cells with small nuclei in alveolar arrangement, with red blood cells in the lumens. In the text reference is made to a number of the older surgeons and pathologists who described similar bulky lesions in bones, which they considered primary vascular endotheliomas. Ewing says that he has seen three such cases, but in a final paragraph he warns that such tumors may be confused with metastases from primary growths elsewhere. Thomas (1942), in his paper dealing with vascular tumors of bone, has apparently been influenced by Ewing, for he includes cases which he calls angio-endothelioma. One of them is illustrated and is Bone Sarcoma Registry Case 2156. It formed a bulky tumor in the humerus. Death followed six months after amputation, apparently from heart disease, and there was no autopsy. The photomicrograph shows a tumor exactly like that illustrated by Ewing.

If these tumors are truly hemangio-endotheliomas they differ histologically from any others in other parts of the body, and must be a variety peculiar to bone. They can be explained more easily as metastases. The histologic structure described and illustrated is exactly like hypernephroid carcinoma. Red blood cells in the lumens of the tubules lined by the characteristic clear cells is not an uncommon finding in the primary kidney tumors. Moreover, a solitary metastasis to bone from an occult hypernephroid carcinoma is a well recognized phenomenon. For these reasons it seems improper to accept such cases as hemangio-endotheliomas or, indeed, as vascular tumors at all.

CASE REPORTS

BREAST

Case 1.—J. M., white female, age 19.

Slightly bluish lumps in the right breast, of three months' duration, were treated

for six months with estradiol benzoate without avail. When biopsy showed what was wrongly interpreted as a capillary hemangioma this was stopped and four months later quinine and urethane were injected into the constantly enlarging breast. Five months after biopsy the enormously enlarged, turgid, discolored breast was removed by Dr. D. C. Bull (Fig. 1). It weighed 1647 Gm. and contained a liter of blood. Two months later metastases began to appear, first in the abdominal wall and later in the humerus, scapula and lungs. Before mastectomy the platelets were low and now

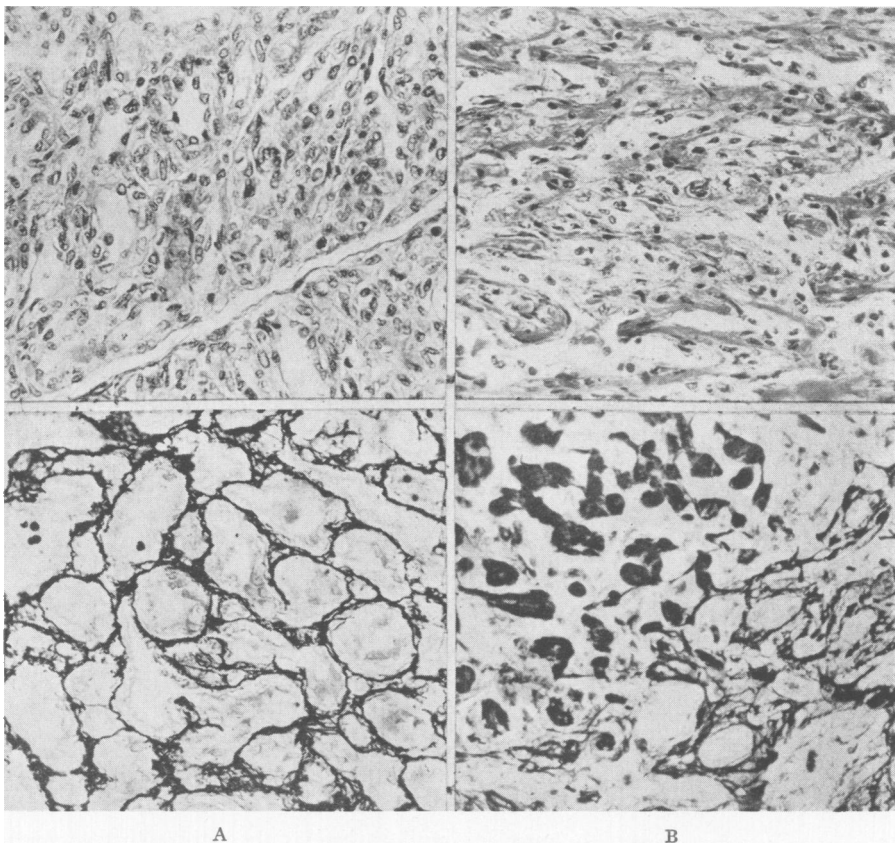


FIG. 5.—Case 17: A (left). Hemangio-endothelioma of scalp. Above are shown the vessels with rounded cells surrounding their lumens. One can only be certain that all the encompassing cells are endothelia by using silver to outline the vascular framework, as shown below.

Case 16: B (right). Hemangio-endothelioma of eyelid. Above, is shown the anastomosing vascular channels lined by elongated hyperchromatic endothelia. Some of these are encased by thick collagenous sheaths as shown by the silver stain below (see Fig. 10). (X 525 reduced)

they dropped to 51,000, and ecchymoses appeared on the legs. Three months after mastectomy she died, with symptoms of abdominal hemorrhage.

The breast was honeycombed with blood-filled cavities of all sizes, and these showed a proliferation of rounded and flattened malignant endothelia sometimes heaped up and sometimes in a single layer, quite comparable to the tumor shown in Figure 2 A. The primary growth showed freely anastomosing capillaries lined by swollen elongated endothelia, comparable to Figure 3 C (Hill and Stout: Sarcoma of the Breast, Case 25, illustrated).

Case 2.—J. M., white female, age 65.

A five-centimeter nodule lateral to the nipple in the right breast, with a reddish-

purple hue to the elevated overlying skin and a suggestion of pigskin effect. Radical mastectomy was performed two weeks after onset, and the firm, grayish-white mass was speckled with areas of hemorrhage and yellow foci. There were no axillary metastases found. Microscopically, the growth resembled Case 1. One month later there were recurrences in the scar and lung metastases. Irradiation was without effect, and two months after onset the patient was dead. (Case of Drs. W. C. Seelye and J. P. Beck, Worcester, Mass. Reported by Hill and Stout: Sarcoma of the Breast, with illustration).

Case 3.—A. P., white female, age 68.

Pain in the right breast of two years' duration and a lump which, after a blow some months before, became black and blue and began rapidly to increase in size. It was said to be the size of an orange when simple mastectomy was performed. One month after mastectomy there was a recurrence in the scar, from which blood was aspirated. Three months after mastectomy there were metastases in both lungs and the right ischium. Numerous skin metastases next appeared over opposite breast and forehead. In spite of irradiation therapy with roentgen-ray and radium she died four months after operation. The breast tumor, examined by Dr. A. O. Severance, was 7 x 4.5 x 3.5 cm., and grossly suggested a hemorrhagic fat necrosis. He correctly diagnosed it as malignant hemangio-endothelioma. It closely resembled the two preceding cases (Fig. 3 C). (Case of Drs. C. S. Venable, D. Jackson, and A. O. Severance, San Antonio, Texas).

LIVER

Case 4.—Autopsy 11340: M. B., colored male, age 54.

This syphilitic patient had been under treatment for diabetes for a year. Seven weeks before death he suffered from abdominal cramps, profuse diarrhea and bloody ascites. He failed rapidly, and died without remission of symptoms. At necropsy, the liver weighed 2740 Gm., and measured 29 x 13 x 23 cm. It was filled with large hemorrhagic nodules and smaller hard yellowish-white ones. Metastases were found in pancreas, kidneys, right suprarenal, spleen, diaphragm, lungs, peritoneum, omentum, abdominal skin and abdominal lymph nodes. Microscopically, the tumor is composed of multiple anastomosing vascular tubes lined by large bizarre endothelia which are heaped up in many places. The multiplication of these cells is so great it obscures the tube formation in some areas but its presence is revealed by the silver reticulin stain. The abdominal skin nodules were found around the punctures of the paracentesis needle and may represent tumor implants. (From the Pathology Laboratory of the Presbyterian Hospital. Dr. J. W. Jobling, Director).

Case 5.—Path. 12177: A. C., male, age 52.

Symptoms began with a dragging pain in the right flank one year before death. It gradually became worse, with radiation to epigastrium, loss of weight, darkening of skin, weakness, dizziness and dyspnea. Except for a large liver, no definite findings were recorded. Following cystoscopy, he developed acute uremia and died in a few days. At necropsy, the liver weighed 3020 Gm., and measured 31 x 19 x 10 cm. It contained multiple large and small nodules of yellowish-red hue, found chiefly in the right lobe. The largest was three centimeters in diameter. Metastases were found in the heart and lungs. The tumor is made up of vascular tubes outlined by reticulin fibers, lined with large, swollen, elongated endothelia of bizarre appearance and variable size and shape, which are not heaped up (similar to Fig. 3 A). (From the Pathology Laboratory of the Presbyterian Hospital. Dr. J. W. Jobling, Director).

BONES

Case 6.—L. D., female, age 60±.

Four months before operation pain began in the region of the left external malleolus

and was soon followed by swelling in the lower leg and ankle but not in the foot. No history of trauma. Roentgenograms showed evidence of a destructive central lesion in the lower ends of the tibia and fibula, with widening of the bones. When the marrow cavities of the lower ends of the tibia and fibula were exposed they were filled with a very vascular tissue which looked like sponge rubber. This was curetted out. The wound was packed open because of oozing, with subsequent secondary closure and

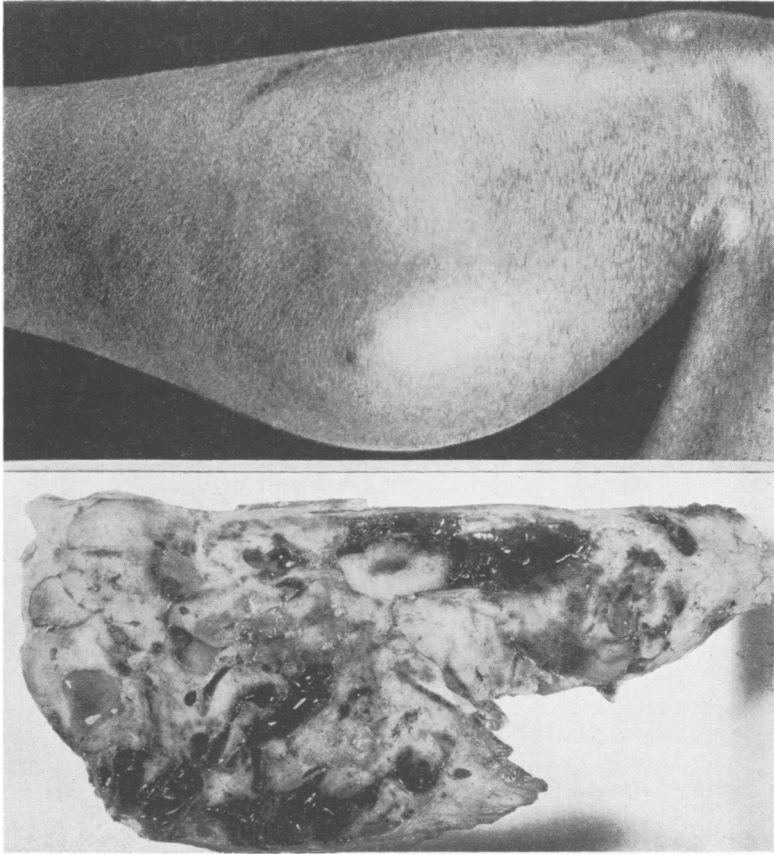


FIG. 6.—Case 9: Hemangio-endothelioma of flexor longus digitorum and flexor longus hallucis muscles in the left calf of a 28-year-old colored male. It was 11.5 cm. larger than the right calf (see Figs. 4B and 7).

FIG. 7.—Case 9: Section of the large tumor showing many hemorrhages, vascular spaces and areas of degeneration (see Figs. 4B and 6).

good healing. Three months after the operation roentgenograms showed what appeared to be an extension of the process in the tibia and fibula and similar areas of rarefaction in all the tarsal and metatarsal bones and a possible area of involvement in the great trochanter of the femur of the same side. She was known to have been alive ten months after operation, but the final result is unknown. The tumor is composed of great numbers of small capillaries which anastomose freely and are lined by prominent hyperchromatic endothelia. These are all elongated and frequently fill and obliterate the lumen. The stroma is often filled with red blood cells. The bony trabeculae show pressure atrophy (Fig. 3 B). (Case of Drs. H. W. Cave, surgeon, and W. Brandes, pathologist of the Roosevelt Hospital, N. Y.).

Case 7.—Young female (20±).

The history of this tumor is not available. It is known to be primary in a rib. It metastasized widely, and killed her in two or three years. The case was studied by Dr. H. E. MacMahon, in the Laboratory of Pathology, Tufts College Medical School, who permits its inclusion in this group. Dr. Frederic Parker called the case to my attention. Histologically, the tumor shows great variability, in some areas the vascular tubes are lined with elongated cells, elsewhere the cells are rounded and heaped-up, and, finally, overproduction of tumor cells in solid masses obscures the vascular tubes.

MUSCLES

Case 8.—J. P., male, age 14.

Eight months before operation this boy fell, striking his side and back. There was not much pain at the time but one week later dull aching in the interscapular region began. It persisted and, finally, a deep mass was felt. Roentgenograms were negative. It was first explored by Dr. W. Darrach, and found to lie in the right erector spinae group of muscles, with its upper end at the level of the spine of T 6. It was dark purple, rubbery, not encapsulated, and about five centimeters in diameter. A biopsy showed that the tumor was malignant, and five days later the mass was excised with the surrounding muscles, but some of it was left behind in the sixth right intercostal muscle. In four months there were evidences of lung metastases and symptoms of paraplegia. Death occurred seven months after operation. This tumor is composed of many vascular spaces outlined by reticulin fibers and lined with both rounded and elongated bizarre endothelia. The vessels are often obscured by an overgrowth of these elongated cells which appear in solid sheets (Fig. 4 A).

Case 9.—M. W., colored male, age 28.

The growth first appeared unexpectedly as a marble-sized lump in the left calf, three years before operation. It was stationary until nine months before when the calf began to swell. Four months before, aspiration yielded only blood. Examination showed a diffuse enlargement of the left calf, which measured 47.5 cm. in circumference, while the right was only 36 cm. (Fig. 6). When a frozen-section showed a malignant tumor, amputation through the middle third of the thigh was performed by Dr. C. D. Haagensen. Eight months later there was no evidence of return. The tumor measured 16 x 13.5 x 6 cm., was exceedingly vascular, with large spaces filled with black, viscid bloody fluid, and lay with the flexor digitorum longus and flexor hallucis longus muscles, from which it had apparently arisen and invaded the overlying soleus and peroneus brevis muscles (Fig. 7). The microscopic picture in this tumor is obscured because of the great degree of overgrowth of elongated endothelia which form apparently solid sheets and cords, with spaces containing red blood cells scattered among them. The Laidlaw silver reticulin stain outlines the vascular tubes (Fig. 4 B), and the diagnosis was made certain by the growth of endothelia from tumor explants *in vitro*, by Dr. Margaret Murray. Details will be given in a separate communication.

UTERUS

Case 10.—A. M. S., married female, age 28.

Thirty-one months before operation she began to have gradually increasing menorrhagia. Seven months before she bled daily for one month. A curettage showed that most of the endometrium was replaced by capillaries, and it was supposed that she had a hemangioma. Bleeding continued, and a month later a second curettage showed persistence of the vascular tumor. During all this time she suffered from attacks of cramping abdominal pain. Just before operation the temperature was 100° F., pulse 140, vaginal bleeding profuse, and there was pain in the chest and cough. At operation, the uterus was soft and enlarged to the size of a three months' pregnancy.

Hemorrhagic implants were found on the lower sigmoid and in the cul-de-sac of Douglas. A supravaginal hysterectomy, right salpingo-oophorectomy, appendicectomy, and biopsy of sigmoid was performed. When the uterus was opened, a reddish, friable tumor mass was found in the endometrium of the fundus. It penetrated the myometrium. Several other similar, but smaller foci were found in the left cornu and on the posterior wall. Nine months later, metastases were found in the left scapula and still later in both lungs, peritoneum and pelvic bones. She became too anemic to tolerate roentgenotherapy. She died 14 months after operation. This tumor throughout its course shows the same histologic picture. It is composed of capillaries lined by

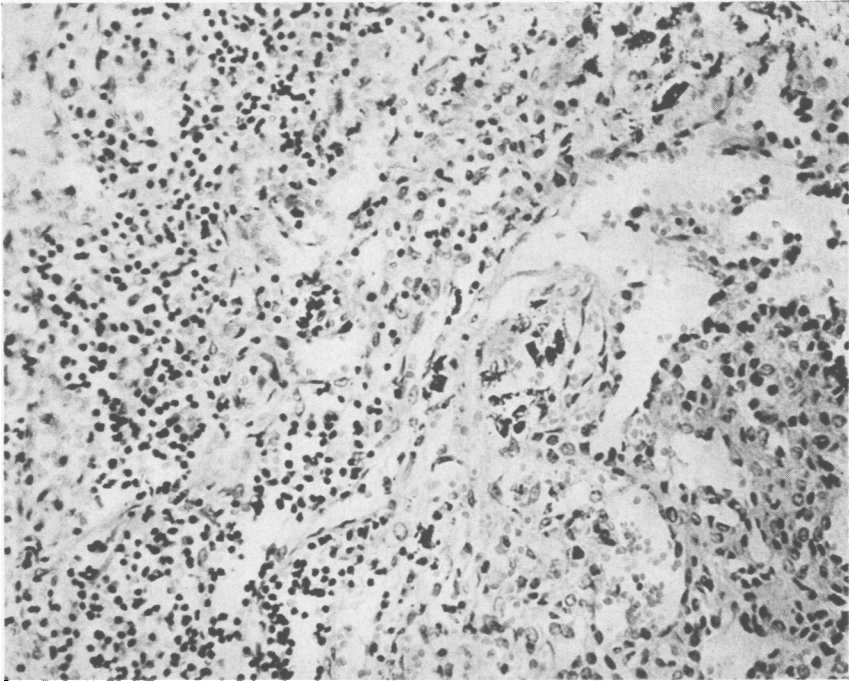


FIG. 8.—Case 11: Hemangio-endothelioma of pleura. Metastasis in a hilar lymph node. Capsule and marginal sinus at left; anastomosing tumor vessels lined with bizarre endothelia at right.

swollen, elongated, hyperchromatic bizarre endothelia showing great variation in size and frequent mitoses. The cells are almost always in a single layer and there is little tendency to heap-up or invade outside the vessel wall. The tumor shows marked infiltrative tendencies (Fig. 3 A). (This case was treated in Sloane Hospital, N. Y., by Dr. B. P. Watson, Director, and is included with his permission).

PLEURA

Case 11.—T. T., male, aged 61.

Eight months before death, pains began in left lower chest, followed by night sweats, weakness and hemoptysis. Two months before death, he entered the hospital, and bloody fluid was repeatedly removed from the left pleural cavity. It was felt that he had a cancer of the lung. After a progressive downhill course he died at the Lincoln Hospital, and was autopsied by Major Chester R. Brown, N. Y., who permits me to include this case. The entire left pleura, both visceral and parietal, was markedly thickened by the hemorrhagic tumor. Metastases were found in the hilar lymph nodes (Fig. 9) and the left lung, and the diaphragm was invaded. In

addition, simple cavernous hemangiomas were found in the diaphragm. This tumor consists, basically, of freely anastomosing vascular tubes lined by atypical endothelia which sometimes are rounded and heaped-up and sometimes flattened, forming a one layer membrane (Fig. 8).

ORBIT

Case 12.—I. P., female, age 40.

She suffered for two years from swelling of the left upper eyelid, with proptosis and double vision during the last three months. Roentgenograms showed an enlargement of the left orbit. At operation, by Dr. G. M. Bruce, a firm mass extended along the roof on the nasal side, from the apex nearly to the anterior orbital margin. Although adherent, it was excised, and measured two centimeters in length. Following this she got a complete paralytic ptosis. Eighteen months later an attempt to correct this by operation failed because of tumor recurrence. A second attempt to excise this was made three years after the first operation. This failed because the growth now infiltrated the medial rectus muscle and the optic nerve. When last seen, six years after the first operation, the globe was fixed and immobile and the ptosis persisted. The tumor appears the same in both manifestations. It consists of freely anastomosing vascular channels occasionally lined by swollen rounded heaped-up endothelia but often obscured by an overgrowth of elongated endothelia. (Case treated at the Institute of Ophthalmology, N. Y., and included by permission of Dr. J. H. Dunnington, Clinical Director).

SUBCUTANEOUS TISSUE AND SKIN

Case 13.—W. R., male, age 25.

For two years there had been a swelling in the right supraclavicular fossa, which slowly increased in size, without symptoms, until three months before operation, when pain radiated from it down to the wrist. This disappeared in three weeks but tenderness remained. When examined it was five centimeters in diameter. At operation, the mass appeared like a dark red plum, and was very vascular. It was excised with an adjacent lymph node. When the nature of the growth was determined and direct invasion of the lymph node recorded, the lymph nodes of the right lower neck were removed. No metastases were found. Thirty-seven months after operation metastases appeared in both ischia, left pubis, L 2, L 4, sternum and 6th rib. These were treated by irradiation, with some improvement, so that the man could continue his work. Four years after operation there were lung metastases. He finally died, five years and two months after operation. There was no autopsy but biopsy of a rib confirmed the fact of metastasis. The tumor is made up of freely anastomosing vascular tubes sometimes lined by a single layer of prominent hyperchromatic, flattened endothelia but usually by rounded, swollen, heaped-up tumor cells of varying size (Fig. 2 A). (Three months after the first operation the case was reported Dr. J. M. Hanford).

Case 14.—H. G., colored female, age 49.

She received a blow on the medial aspect of the left knee region two years before admission. This was immediately followed by ecchymosis. Two months later attacks of throbbing pain began and lasted for 16 months, when swelling began, and all symptoms grew worse. Examination showed a diffuse swelling of the posteromesial aspect of the left popliteal region. There were extensive varicosities in this extremity. The lesion was explored, and a large multilocular cystic cavity found containing from 300 to 400 cc. of old blood. It was supposed to be a hematoma. The blood was evacuated and the wound closed. Later, it broke open again and drained foul-smelling bloody material, while the pain and swelling increased. Ten months later, at a second operation, by Dr. A. H. Blakemore, a tumor eight centimeters in diameter was found. It was subcutaneous, sharply circumscribed, and involved the deep fascia. It was excised.

Sixty-seven months after excision there was no evidence of recurrence. The tumor consisted of a spongy mass of intercommunicating cavities filled with blood. A thick-walled vein entered the upper pole of the mass (Fig. 9). Microscopically, this tumor shows numerous vascular tubes which often anastomose and are lined by heaped-up rounded endothelia. In many areas the endothelia have multiplied to such an extent that the lumens are solidly filled, and only the silver reticulin stain demonstrates them by accentuating the fibrous framework (Fig. 2 B).

Case 15.—Female, age 35.

Seven months before operation several nodules developed in the scalp above the right ear. These were diagnosed as "cysts," and biopsy is said to have been taken but no report is available. Soon after, swellings appeared in the right neck. All were firm, circumscribed and somewhat painful and tender. A neck mass, midway between angle of jaw and clavicle, was explored. It was apparently encapsulated, 3 x 2 x 0.5

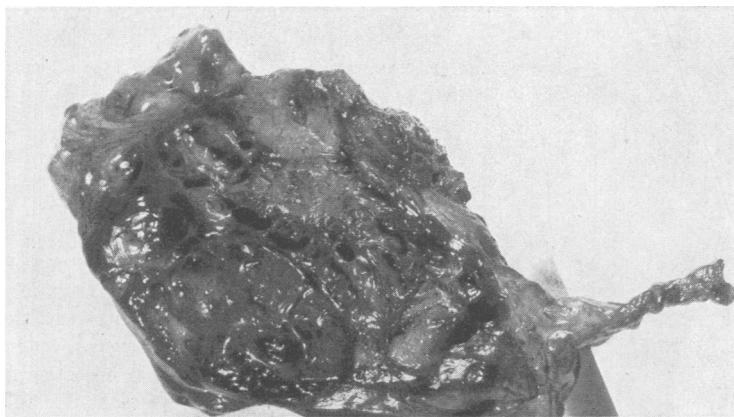


FIG. 9.—Case 14: Hemangio-endothelioma of popliteal region. Cross-section of the tumor tissue, its multiple cavities and the large vein, which entered its upper pole shown at the right (see Fig. 2B).

cm., and lay deep to, but not attached to, a branch of the cervical plexus. It was described as hemorrhagic. The patient was not followed. The tumor is composed of the usual widely anastomosing vascular spaces lined by rounded and polygonal cells, often heaped-up and sometimes forming papillary processes. (Case from the Hospital of the University of Pennsylvania. Reported by permission of Drs. Louis Kaplan, surgeon, and R. H. Horn, surgical pathologist).

Case 16.—S. K., female, age 17.

Ever since birth there had been a "hemangioma" of the lateral aspect of the right upper eyelid. Prior to her first operation, at the Presbyterian Hospital, there had been six previous attempts at surgical removal, all of which failed. At this time, the tumor measured 15 x 10 x 5 mm. It was excised but promptly recurred (Fig. 10). The 8th and 9th attempts were made, respectively, one year and 16 months after the 7th attempt. She was not followed after this last operation, when she was 20 years old. Grossly, the tumor was composed of firm hemorrhagic tissue. This tumor is made up in part of large, cavernous vascular spaces filled with blood and in part of a spongy meshwork of very freely anastomosing capillaries lined by swollen elongated endothelia frequently heaped-up in layers. The capillary sheaths are sometimes greatly thickened and seemingly hyalinized (Fig. 5 B). (From the Ophthalmological Service of the Presbyterian Hospital. The late Dr. John M. Wheeler, surgeon).

Case 17.—W. W., female, age 3 months.

A red spot was present at birth in the skin of the right parietal region. It was one centimeter in diameter and increasing rapidly in size when it was excised. It lay in the skin and did not seem to have any deep connections. No recurrence after 30 months. The growth infiltrates the structures of the skin quite freely without destroying them. It consists of numerous closely placed blood vessels lined with heaped-up rounded endothelia, the most internal layer of which tend to be elongated. This makes it appear in ordinary stains as if the vessel is surrounded by pericytes. Because of this the tumor at first was called a hemangiopericytoma (Stout and Murray, 1942, Case 3). The silver reticulin stain shows that all of the cells are inside of the reticulin sheaths and are, therefore, endothelia (Fig. 5 A). (From the Nix Hospital, San Antonio, Texas. Drs. L. J. Ross, surgeon, and A. O. Severance, pathologist).

Case 18.—D. R., male, age 11 months.

When the child was three months old, the mother noted a swelling over the inner angle of the left eyebrow. Slow increase to 25 mm. diameter. It was subcutaneous, with normal overlying skin, and was mistaken for a dermoid cyst. No recurrence one year after excision. Microscopically, the growth exactly resembles Case 17, except that it is subcutaneous instead of intradermal. Only a few of the vessels have visible lumens containing red blood cells, because multiplication of the endothelia has solidly filled them. The silver reticulin stain shows the true state of affairs. (Case from Babies Hospital, Dr. B. Paige, pathologist).

SUMMARY

Hemangio-endothelioma is the most common type of the malignant vascular tumors but, even so, it is a relatively rare neoplasm. It has a wide distribution in the various organs and tissues of the body, and may manifest itself at any age, although half of the cases occur in childhood or youth. Growth may be rapid or slow, and is infiltrative in character. When approached, the tumors are usually, but not always, obviously vascular, with a tendency to bleed into themselves or from the surface. Metastasis is common and is generally through the blood stream although occasionally it progresses also through the lymphatics.

The tumors are made up of congeries of vascular tubes which have a marked tendency to anastomose and are lined with hyperchromatic atypical endothelial tumor cells. These may be of any shape and size. They may form a single layer, be heaped-up in several layers, or even multiply to such a degree that the vascular tubes are completely obscured, when ordinary stains are used, and can only surely be demonstrated by silver connective tissue impregnations. The same tumor may show two or more of these variations in the primary growth and the metastases. No tumor should be called a hemangio-endothelioma unless it fulfills these microscopic criteria and, conversely, if a tumor does show these characteristics it should be recognized as a malignant or potentially malignant tumor. There is no such anomalous entity as a benign metastasizing hemangioma. Two other tumor forms especially have been confused with this one, namely, chorio-epithelioma and hypernephroid carcinoma. If the criteria already given are strictly applied, one should be able to avoid this error. The hemangio-endothelioma of

infants apparently is better differentiated and probably less malignant, although it may kill by the multiplicity of its tumors, as occurred in Wollstein's case. The silver reticulin stain is of particular assistance in aiding one to distinguish hemangio-endothelioma from hemangiopericytoma, since endothelia are found inside and pericytes altogether outside the reticulin sheath of the vessels. Demonstration that tumor cells behave *in vitro* like endothelia provides further confirmatory evidence.



FIG. 10.—Case 16: Hemangio-endothelioma of the right eyelid in an 18-year-old girl. It was present at birth, and seven previous operations had failed to eradicate it (see Fig. 5B).

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